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Application for Patent

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אני, (שם המבקש, מענו -- ולגבי גוף מאוגד -- מקום התאגדותו)
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(בעברית) (Hebrew): מתקן לכיול מנתח גזים

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מבקשת פטנט from Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האיגוד Convention Country
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מתקן לכיול מנתח גזים

GAS ANALYZER CALIBRATION DEVICE

ORIDION MEDICAL LTD. אורידיון מדיקל בע״מ

C:34070

GAS ANALYZER CALIBRATION DEVICE

FIELD OF THE INVENTION

The present invention relates to the field of gas analyzer calibration and filtering devices, especially for use with breath test instrumentation.

BACKGROUND OF THE INVENTION

Gas analyzers are used for many measurement and monitoring functions in science, industry and medicine. In particular, gas spectrometry is becoming widely used in diagnostic instrumentation based on the use of breath tests for detecting a number of medical conditions present in patients. Such breath tests are now becoming widely used, and a review of many of the methods and instrumentation described in the prior art is contained in the background section of PCT Publication No.WO 99 / 12471, entitled "Breath Test Analyzer".

These breath tests are based on the ingestion of an isotopically labeled substrate, which is cleaved by the specific bacteria or enzymic action being sought, or as a result of the metabolic function being tested, to produce isotopically labeled gaseous by-products. These by-products are absorbed in the blood stream, and are exhaled in the patient's breath, where they are detected by means of the gas analyzer.

A commonly used atom in such test procedures is the non-radioactive carbon-13 atom, present in a ratio of about 1.1% of naturally occurring carbon. The cleavage product produced is $^{13}CO_2$, which is absorbed in the bloodstream and exhaled in the patient's breath. The breath sample is analyzed, before and after taking the isotopically-labelled substrate, usually in a mass spectrometer or a non-dispersive infra-red spectrometer. Any increase in the ratio of $^{13}CO_2$ to $^{12}CO_2$ detected is taken as a quantitative measure of the presence of the specific bacteria or enzymic action being sought, or as a measure of the metabolic function being tested.

Since the amount of CO_2 arising from the metabolic process under test may be a very small proportion of the total CO_2 production from all of the bodies' metabolic processes, the breath test instrumentation must be capable of detecting very small changes in the naturally occurring percentage of $^{13}CO_2$ in the patient's breath. Typically, the instrument should be capable of detecting changes of a few parts per million in the level of $^{13}CO_2$ in the patient's exhaled breath. For this reason, the sensitivity, selectivity and stability of the gas analyzers used in such tests must be of the highest possible level to enable accurate and speedy results to be obtained.

In order to maintain the reliability of such tests, it is necessary to ensure that the calibration of the gas analyzer is maintained at the correct level. For this reason, in order to ensure maintenance of the high accuracy levels required, many of the prior art instruments necessitate the performance of complex and time-consuming calibration procedures, some of which have to be laboratory performed, rather than user-performed in the field. Since the advent of compact and low cost breath test instrumentation is making breath testing a widely used medical office procedure, instead of the hospital or laboratory procedure which it previously was, the need for simple, user-performed, mandated periodic calibrations and calibration verifications is becoming of prime importance. The term calibration is used in this specification to refer to a measurement of the absolute calibration of the isotopic ratios measured by the breath tester, refered to a zero base line level. A calibration verification is a single point check of the isotopic ratio of a sample.

Furthermore, the breath exhaled by patients always contains a naturally high level of moisture, and in the case of intubated patients, could also contain a high level of other secretions. The presence of such extraneous fluids can severely affect the ability of the gas analyzer to accurately measure the sought-after gas. Furthermore, constant exposure to high levels of moisture can have an adverse effect on the component parts of the gas analyzer, and especially on the measuring sensor itself. For these reasons, moisture and humidity filters

are essential to maintain the accuracy of the instrument. Since the operator may have a tendency to use the filters provided with the instrument beyond the recommended number of times, thereby impairing the accuracy of the measurement, it is important that means be adopted to ensure that the filtration unit is not used beyond its stated lifetime.

There therefore exists a serious need to ensure the maintenance of the accuracy of breath test instrumentation, both by means of regular mandated calibration checks, and by ensuring regular mandated changes of the moisture filter used with the instrument. Furthermore, there is a need for the calibration procedure to be capable of simple and preferably automatic execution by the user, rather than requiring the intervention of a technician, or shipment to a calibration laboratory.

The disclosures of all publications mentioned in this section and in the other sections of the specification, and the disclosures of all documents cited in the above publications, are hereby incorporated by reference.

SUMMARY OF THE INVENTION

The present invention seeks to provide a new calibration device for use with gas analyzer based breath test and capnographic instrumentation. The use of the device with breath tests is particularly important, because of the high sensitivity, selectivity and accuracy, which must be maintained to ensure the success of such tests. The use of the device is simple, and ensures that the accuracy of the gas analyzer is checked at regular predetermined periods, without the need for the operator to perform complex calibration procedures. At the same time, the calibration device may also comprise a fluid filter, and is so constructed that use of the calibration device ensures efficient fluid filtering.

There is thus provided in accordance with a preferred embodiment of the present invention, a self-calibrating sampling line unit with an integral filter, particularly for use with breath test instrumentation. In order to maintain the

guaranteed accuracy of the breath test, it is important both to perform regular calibrations of the gas monitor, and to ensure that the humidity level of the sampled gas is kept below a specified level, and that there is no liquid penetration into the gas analyzer. Each calibration device is designed to be used for a predetermined number of tests, with a separate disposable oral/nasal part for each individual test performed. After first connection of a new calibration device, a premeasured volume of calibration gas is released into the instrument, and a calibration measurement is initiated. At the same time, an signal is sent to a counting mechanism which both enables the use of the instrument, and commences a count of the number of tests performed by the breath tester. The counting mechanism can be located either on the calibration device or in the instrument itself. When the predetermined number of tests have been performed, after which a new calibration is recommended, the counting mechanism provides operator warning thereof, or preferably even prevents continued operation of the instrument until a new calibration is performed. According to another preferred embodiment of the present invention, the signal transmitted after first connection of a new calibration device and performance of a calibration procedure, is sent to a timing mechanism which both enables the use of the instrument, and begins accumulating the amount of time that the breath tester has been in operation since the last calibration procedure. When a predetermined operation time has been exceeded, after which a new calibration is recommended, the timer mechanism provides operator warning thereof, or preferably even prevents continued operation of the instrument until a new calibration is performed.

According to a further preferred embodiment of the present invention, the built-in moisture filter also has an interface with the instrument, which prevents its operation if the filter is used beyond the recommended number of times, or if excess moisture renders it saturated. As an alternative to a multiple-use filter unit, the disposable oral/nasal part supplied for each individual test could be provided with a built-in section of moisture filtering or moisture absorbing material, to ensure the use a fresh filter element for every patient test. According to this

embodiment of the invention, the use of a fresh filter, while not mandated, will be performed automatically if normal hygienic clinical procedures of using a new cannula for every test are followed. This would be evident to a patient if requested to insert a plastic cannula into his mouth or nose. In this case, to give additional assurance that a new cannula would be used for every test, each calibration unit would be supplied as a kit with the number of disposable oral/nasal parts, which would suffice for the number of tests expected to be performed within the recommended changing period of the calibration unit.

In accordance with further preferred embodiments of the present invention, where the particular circumstances of the test conditions allow it, the calibration device can incorporate a calibration unit only, without a filter device, or a filter device only, without any calibration unit. Alternatively and preferably, the calibration device can contain both a calibration unit and a filter unit, and the enable or count signal transmitted to the instrument from only one or other of the two units.

In accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer, consisting of a calibrating unit, and an enabling mechanism for enabling operation of the gas analyzer.

There is further provided in accordance with yet another preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the enabling mechanism is operative to count the number of tests performed by the gas analyzer.

In accordance with still another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer as described above and wherein the enabling mechanism is operative to accumulate the time of operation of the gas analyzer.

In accordance with a further preferred embodiment of the present invention, there is also provided a calibration device for use with a gas analyzer as described above and also consisting of a filter for removing fluids from a gas

to be analyzed.

There is provided in accordance with yet a further preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the enabling mechanism for enabling operation of the gas analyzer is operated by the calibrating unit.

There is even further provided in accordance with a preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the enabling mechanism for enabling operation of the gas analyzer is operated by the filter.

In accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas as described above and wherein the enabling mechanism is communicative with the gas analyzer by means of a signal selected from a group including electrical, electronic, optical, mechanical, magnetic and gaseous signals.

Furthermore, in accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer, consisting of a calibrating unit, and a count actuating mechanism initiated by first use of the calibration device, operative to begin a count of the number of tests performed with the calibration device.

There is also provided in accordance with a further preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and also consisting of a filter for removing fluids from the gas to be analyzed.

In accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer as described above and wherein the count actuating mechanism is actuated by the calibrating unit.

There is further provided in accordance with yet another preferred embodiment of the present invention calibration device for use with a gas analyzer as described above and wherein the count actuating mechanism is

actuated by the filter.

In accordance with still another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer as described above and wherein the count is used to prevent use of the gas analyzer after a predetermined number of tests have been performed.

There is further provided in accordance with still another preferred embodiment of the present invention a calibration device for use with a gas as described above and wherein the count of the number of tests performed with the calibration device is performed within the gas analyzer.

In accordance with a further preferred embodiment of the present invention, there is also provided a calibration device for use with a gas analyzer as described above and wherein the count of the number of tests performed with the calibration device is performed within the calibration device.

There is provided in accordance with yet a further preferred embodiment of the present invention a calibration device for use with a gas as described above and wherein the enabling mechanism is communicative with the gas analyzer by means of a signal selected from a group including electrical, electronic, optical, mechanical, magnetic and gaseous signals.

There is even further provided in accordance with a preferred embodiment of the present invention calibration device for use with a gas analyzer analyzer as described above and wherein the calibrating unit releases a calibration gas of known composition into the gas analyzer.

In accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer as described above and wherein the enabling mechanism is actuated by release of the calibrating gas.

Furthermore, in accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas as described above and wherein the calibrating unit releases a calibration gas of known composition into the gas analyzer.

There is also provided in accordance with a further preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the count actuating mechanism is actuated by release of the calibrating gas.

In accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas as described above and wherein the enabling mechanism is actuated by means of an active integrated circuit disposed on the calibration device

There is further provided in accordance with yet another preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the count actuating mechanism is actuated by means of an active integrated circuit disposed on the calibration device

In accordance with still another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer as described above, and also consisting of a disenabling device which prevents the count actuating mechanism from being reinitiated after first use of the calibration device.

There is further provided in accordance with still another preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the filter is a section of a sampling tube having built-in fluid filtering properties.

In accordance with a further preferred embodiment of the present invention, there is also provided a calibration device for use with a gas analyzer as described above and wherein the built-in fluid filtering properties are supplied by means of a drying agent disposed in proximity to at least part of an inside wall of the sampling tube.

There is provided in accordance with yet a further preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the construction of the calibration unit and the fluid

filter are such as to essentially maintain the waveform of a breath of gas to be analyzed.

There is even further provided in accordance with a preferred embodiment of the present invention a calibrating unit for use with a gas analyzer, consisting of a sampling line for conveying a gas to be analyzed to the gas analyzer, at least one enclosure housing at least one container of calibrating gas, at least one mechanism for releasing the calibrating gas in the at least one container into the enclosure, the mechanism having interactive control contact with the gas analyzer, and at least one delivery conduit connecting between the enclosure and the sampling tube for conveying the calibrating gas after release into the sampling line.

In accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer as described above and wherein the interactive control contact consists of the actuation of the mechanism by means of the gas analyzer

Furthermore, in accordance with yet another preferred embodiment of the present invention, there is provided a calibration device for use with a gas analyzer as described above and wherein the interactive control contact consists of the transmission of a signal to the gas analyzer on actuation of the mechanism. There is also provided in accordance with a further preferred embodiment of the present invention a calibrating unit for use with a gas analyzer as described above, and wherein the at least one container of calibrating gas consists of two containers of calibrating gas.

In accordance with yet another preferred embodiment of the present invention, there is provided a calibrating unit for use with a gas analyzer as described above, and wherein the at least one delivery conduit consists of two delivery conduits.

There is further provided in accordance with yet another preferred embodiment of the present invention a calibrating unit for use with a gas analyzer, consisting of a calibrating gas mixture consisting of at least a first and a

second gas, and a delivery conduit for conveying the calibrating gas mixture to the gas analyzer, the delivery conduit consisting of a material which allows preferential diffusion through its wall of at least one of the at least a first and a second gas.

In accordance with still another preferred embodiment of the present invention, there is provided a calibrating unit for use with a gas analyzer as described above, and wherein the material is a selective membrane.

There is further provided in accordance with still another preferred embodiment of the present invention a calibrating unit for use with a gas analyzer as described above, and wherein the material is a porous diffusive tube.

In accordance with a further preferred embodiment of the present invention, there is also provided a kit for calibration of a gas analyzer consisting of at least one calibrating unit according to any of the previous claims, and a plurality of disposable sampling tubes for each of at least one calibrating unit.

There is provided in accordance with yet a further preferred embodiment of the present invention a kit for calibration of a gas analyzer as described above, and wherein at least one of the sampling tubes consists of a fluid filter.

There is even further provided in accordance with a preferred embodiment of the present invention a kit for calibration of a gas analyzer consisting of at least one calibrating unit capable of interactive communication with the gas analyzer, and a plurality of disposable sampling tubes for each of the at least one calibrating unit.

In accordance with yet another preferred embodiment of the present invention, there is provided a kit for calibration of a gas analyzer as described above, and wherein at least one of the sampling tubes consists of a fluid filter.

Furthermore, in accordance with yet another preferred embodiment of the present invention, there is provided a calibrating unit operative to generate a second calibration material from a first material input thereto.

There is also provided in accordance with a further preferred embodiment of the present invention a calibrating unit as described above and wherein the first material is also a calibrating material.

There is also provided in accordance with a further preferred embodiment of the present invention a calibrating unit as described above and wherein the materials are gases for use in a gas analyzer.

In accordance with yet another preferred embodiment of the present invention, there is provided a breath bringer which changes a characteristic during use.

In accordance with still another preferred embodiment of the present invention, there is provided a breath bringer as described above, and wherein the characteristic is a color.

There is further provided in accordance with still another preferred embodiment of the present invention a calibration device for use with a gas analyzer as described above and wherein the enabling mechanism is operative to accumulate the time since last calibration of the gas analyzer.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be understood and appreciated more fully from the following detailed description, taken in conjunction with the drawings in which:

Fig. 1 illustrates schematically a gas analyzer calibration device, constructed and operative according to a preferred embodiment of the present invention, connected to a breath tester;

Figs. 2A and 2B are schematic cut-away illustrations of preferred connector embodiments for interfacing between the gas analyzer calibration device, and a breath testing instrument, where Fig. 2A is of a connector incorporating a simple electrical contact interface and Fig. 2B is of a connector

with an optical interface. Fig. 2C is a block diagram of the method of interfacing an electronic interface which incorporates an active semiconductor integrated circuit, on the calibration unit connector;

Fig. 3 is a schematic representation of another preferred embodiment, in which the filter function is performed by means of a dedicated section of the disposable oral/nasal cannula sampling tube, which has built-in filtering properties;

Fig. 4 is a schematic illustration of an integral sampling filter line whose filter section is preferably one of those described in U.S. Patent No. 5,657,750;

Fig. 5 is a cut-away schematic diagram of an embodiment of the calibration unit, showing a glass ampoule containing premixed calibration gases;

Fig. 6A and 6B are cut-away schematic diagrams of two preferred embodiments of calibration units, with two glass ampoules, each containing premixed calibration gases;

Fig. 7 is a schematic view of a preferred embodiment of a gas calibration unit, based on the use of a section of tubing constructed of a selectively porous membrane, or of a porous diffusive tube, which allow preferential diffusion from the air of $^{12}CO_2$, as compared with $^{13}CO_2$; and

Fig. 8 is a schematic illustration of a porous diffusive tube suitable for use in the embodiment shown in Fig. 7.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Reference is now made to Fig. 1, which illustrates schematically a gas analyzer calibration device 10, constructed and operative according to a preferred embodiment of the present invention, connected to a breath tester 12. The device consists of two separate components, the calibration unit 14, and the fluid filter unit 16. The patient 18 is connected to the device by means of a disposable nasal or oral sampling tube 20, into which he breathes. This sampling tube is connected to the filter unit 16 of the device by means of a mating connection 22. The

sampling tube is of a simple nasal/oral cannula type, such that it is a low cost disposable item.

The filter unit 16 is attached to the calibration unit 14, or is constructed as an integral part thereof, such that the exhaled breath, after having moisture removed from it, passes through the calibration unit 14, into the gas analyzer section 28 of the breath tester 12. The complete gas analyzer calibration device 10 is connected to the breath tester by means of a special flange connector 24, whose function is twofold. Firstly, it provides passage of the exhaled breath to be tested into the gas analyzer 28. In addition, it provides one or more of electrical, electronic, optical, magnetic, gaseous and mechanical interfaces, according to the particular embodiment used, between the gas analyzer calibration device and the breath tester.

The interface mechanism fitted to the calibration unit is preferably such that the first time it is connected to the breath tester, a momentary signal is inputted by means of control line 15 to a controller unit 26 within the breath tester 12, which resets an accumulator unit which counts the number of breath tests performed with each calibration unit. The actual count is performed by the breath tester program, and a count could be added to the total, for example, for every occasion that the "Start Test" command is given to the system.

According to a further preferred embodiment of the present invention, the controller unit 26 within the breath tester 12 is operative to start a timing device which accumulates the total time of operation of the breath tester from first connection of a specific calibration device. In this embodiment, the criterion for use of one calibration device is not the number of tests performed using it, but rather the length of time the breath tester is in operation before a calibration check is considered necessary.

According to another preferred embodiment of the present invention, the signal to reset the test counting mechanism to zero could be provided by the entry of the calibrating gas itself. According to this embodiment, the analyzer is programmed to detect that the gas entering its input port does not have a

conventional breath waveform, and the system thus assumes that the gas entering is from a calibration procedure. Alternatively, a marker gas could be included with the calibration gas, and detected by the gas analyzer.

The filter unit, according to other preferred embodiments of the present invention, may also have an interface control connection 17 to the controller unit 26 within the breath tester 12. This control signal could be used for instance, for warning the user when the filter unit is saturated and no longer efficient, or even to prevent operation of the instrument, even before its replacement is mandated by the time or number of tests performed. For instance, an accidental ingestion of fluid into the sampling tube from the patient before commencement of the breath test, may render the filter useless for continued use, and without a warning to this effect, the subsequent breath test would be unreliable.

Fig. 2A shows a cut away drawing of a connector incorporating a simple single-use electrical contact interface. The connector flange 30 on the calibration fluid filter device is screwed by means of a knurled nut 32 onto the mating connector flange 34 mounted on the input panel 36 of the breath tester enclosure 38. An O-ring ensures gas tight closure. Once the connector is closed, the gas being analyzed 40 can flow via the calibration unit into the gas analyzer of the breath tester. Mounted on a machined hollow or groove in the mating surface of the flange is a thin metallic foil 42, which, on first instantaneous contact with the connector, touches two contact pins 44. This closes an input signal circuit 46 in the controller unit, thereby enabling the commencement of the count of the number of tests performed with that particular calibration unit installed. However, on screwing the connector completely home, the foil is ruptured, such that subsequent disconnection and reconnection of the calibration unit will not remake the contacts 44, and the clock count cannot therefore be reset to zero using that calibration unit connector. In this way, it is impossible for the operator to attempt to use each calibration unit beyond the recommended number of times by attempting to reconnect it anew after expiry.

Fig. 2B shows a simple optical interface, which operates in a similar way

to the electrical interface shown in Fig. 2A. The trigger signal 58 to commence counting is given by means of the reflection of a light signal transmitted from a source 50 such as a LED, located in the breath tester flange of the interface connector, off a reflective surface such as a metallic foil 52 located in the calibrator flange of the connector, and back to a detector 54 located on the breath tester side. Re-use of the calibration unit after expiry is prevented by a mechanism designed to degrade the reflective properties of the calibrator connector surface so that after first connection, the unit no longer delivers the required signal if reconnected. In the embodiment shown in Fig. 2B, a projection or pin 56, which tears the reflective foil, fulfills this function. Mechanisms similar to those described in Figs. 2A and 2B can be proposed using magnetic or mechanical interfaces for ensuring that the calibration unit can only be connected once to the breath test unit in an unused state.

Fig. 2C now shows block diagrams of methods of interfacing an electronic interface, which incorporates an active semiconductor integrated circuit on the calibration unit. A storage device such as a commercially available smart card can be used, to allow an identification of a specific calibration unit through appropriate communication. The same storage device could also be used to store information relevant to the calibration process such as instrument serial number, calibration date, number of performed tests. The storage of the instrument number could be used to prevent the storage device from being mistakenly used with another instrument, which had not been calibrated.

The IC can function in a number of alternative modes. According to one preferred embodiment, shown in Fig. 2C (ii), the count of the number of tests performed by the particular calibrator is performed and stored in the IC itself. According to another preferred embodiment shown in Fig. 2C (i), the IC does not play any part in the counting procedure, but simply has a code, which is unique to the particular calibrator unit to which it is attached. On first connection to a breath tester, this code is interrogated, and is stored in the count register of the breath tester. So long as the permitted number of tests with that particular code

number has not been exceeded, the breath tester allows another test to be performed.

Communication between the IC in the calibrator unit and the breath tester can be achieved either by a multipin connector, which is engaged when the calibrator unit is attached to the breath tester, or by means of a radio link, or by any other suitable connection means. In the case of a radio link, there is no need to use a special flange on the calibrator unit and breath tester.

The above embodiments have been described in terms of an interface designed to commence a count of the number of breath tests that can be performed after each new calibration unit has been used. According to yet further embodiments of the present invention, the interface flange can be constructed to provide an interface between the filter unit and the controller circuit, such that the filter unit is the element which actuates the count as to the specified number of breath tests permissible before stopping operation of the tester until filter replacement is made. The design of the flange could then be identical to that shown in Figs. 2A and 2B, except that the circuit closing elements are associated with the filter unit.

According to yet another preferred embodiment, the filter unit can be constructed to provide a warning signal to the controller circuit through the interface flange if the absorbed moisture rises to a level above which the filter no longer operates satisfactorily, even before the permitted number of breath tests has been performed with it. In this way, the filter function is doubly protected, both in terms of frequency of replacement, and in terms of efficacy.

Reference is now made to Fig. 3, which illustrates schematically a calibrating fluid filter device 11, constructed and operative according to another preferred embodiment of the present invention. According to this embodiment, the filter unit is of low cost, simple construction, such that it is intended to be an integral part of the sampling tube 62, and is, therefore, disposable like a regular sampling tube. In Fig. 3, the filter is a section 60 of the sampling tube, designed to dry the gas by absorbing moisture, such as by coating the inside walls 61 with a

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sample line with filter section is used, being connected to the calibration unit by means of a connection 22. The electronic interface for preventing operation of the instrument is then operative only from the calibration unit. As in the previous embodiments described, the calibration unit 14, is preferably interfaced with the breath tester 12 by means of a "smart" connector 24, which allows control of the number of breath tests performed with each calibration unit.

If a capnographic measurement is to be made of the breath exhaled by the patient, it is important that the waveform of the breath be maintained in passage through the filter unit, to ensure an accurate capnographic measurement. The preferred embodiment shown in Fig. 3 fulfills this requirement, since the gas flow down the sample tube flows in a smooth laminar manner without any significant obstructions or perturbations, and without any pockets or corners of void volume which could disturb the waveform.

Alternatively and preferably, any of the fluid filtering devices described in U.S. Patent No. 5,657,750 could also be used for this purpose. The filters described in that Patent are constructed so as to avoid significant disturbance to the waveform. Fig. 4 illustrates an integral sampling filter line 63 whose filter section 64 is preferably one of those described in U.S. Patent No. 5,657,750. The sampling filter line is attached to the calibration unit by means of the flange 22.

According to another preferred embodiment of the present invention, the filter unit can be constructed with a color marker which changes color when the filter is saturated, thus providing the user with visible warning that the filter should be replaced, even before the permitted number of breath tests has been performed with it, and the instrument interface prohibits its further use.

Reference is now made to Figs. 5 and 6, which show cut-away schematic diagrams of calibration units, constructed and operative according to preferred embodiments of the present invention. The calibration units incorporate one or more containers of a premixed calibration gas, and can be used in any of the calibration devices described in the previous embodiments, regardless of which

filter configuration is used. With one exception, the calibration units are in interactive control contact with the gas analyzer control system, such that either they cannot be used without transmitting a start signal to the control system of the gas analyzer, or they themselves are actuated by means of a control signal received from the gas analyzer control. The one exception is the embodiment wherein detection of the calibration gas itself by the gas analyzer provides the start signal for the counting or timing process for use of that particular calibration device.

The operation of the calibration units is described for use with a breath test for the detection of changes in the level of $^{13}CO_2$ in the patient's breath, after ingestion of a ^{13}C-labeled substrate. It is to be understood, however, that the units can be equally well applied for use in breath tests with other isotopically replaced atoms, such as nitrogen-15 and oxygen-18.

In the embodiment shown in Fig. 5, the calibration unit housing 70 incorporates a glass ampoule 72 containing the calibration gas, though it could be provided in any form of container capable of being hermetically sealed yet easily opened on demand, such as a metallic cylinder with a foil seal or a depressable check valve. The calibration unit is connected through a narrow bore tube 84 by means of a T-connector 86 into the sampling line 78, which is connected to the breath tester by means of an interface connector 76, such as those described in relation to Figs. 2A to 2C. In the preferred embodiment shown, a plunger 82 is incorporated in the wall of the calibration unit housing 70, such that when the plunger is depressed, the ampoule is broken and the calibration gas mixture released.

The long narrow bore tube 84 now acts as a flow restrictor to prevent the calibration gas from being released too rapidly into the sampling line 78. This ensures that no overpressure effects are produced in the sampling line. An overpressure may overcome the effect of the system vacuum pump located in the breath tester, and allow some of the calibration gas to escape from the system via the patient's end of the sampling line. Furthermore, the delivery of the calibration

gas in sidestream fashion to the sampling line via a T-connector avoids any significant disturbance to the breath waveform, since the small entry hole and the long narrow bore connection tube do not present any appreciable perturbation or void volume to the sample gas flow. This is very important for use with any instrument in which capnographic measurements must be made, in order to avoid damage to the waveform of the breath.

Alternative and preferable methods of releasing the calibration gas include solenoid plungers electrically operated on demand by the breath tester calibration program, or mechanical needles or projections incorporated into the breath tester input flange, which cause mechanical breakage of the gas container seal or depression of a check valve on the calibration gas cylinder as the calibration unit flange is screwed home onto the breath tester flange. If the plunger is designed to be depressed manually, this action can also preferably cause it to send a control start signal to the gas analyzer.

When the time comes to perform a calibration, a new calibration unit, with or without a filter unit attached, is connected to the breath tester. No subject should be connected to the sample tube, since natural air from the environment is required for the calibration procedure. The ampoule of calibration gas is broken, either by operation of the plunger, or by another of the methods mentioned above, or by any other suitable method, and the calibration gas allowed to mix with the incoming stream of ambient air, and to enter the breath tester.

The ampoule contains a known volume of CO_2 such that, with the flow rate ingested by the breath tester, the final percentage of CO_2 in the ingested gas is of the order of 3%, which is the close to the chosen concentration of operation of the gas analyzer. This level can be achieved, for instance, by defining the volume of gas in the ampoule such that when diluted by the known flow rate of the instrument, the correct concentration is achieved, or by means of an intermediate chamber system, such as that described in PCT Publication No. WO 99/12471. Since the volume of the intermediate cell described in PCT Publication

No. WO 99/12471 is of the order of 300ml., then the ampoule should have a volume of 9 ml of 100% CO_2 to ensure that the 3% CO_2 intermediate cell concentration is reached. If a typical flow rate of 250 ml/min. is ingested, the chamber should be full of gas ready for the measurement in a little over 1 minute.

It should be emphasized here that it is not necessary to achieve the exact target CO_2 concentration level for calibration. The important factor for achieving accurate calibration is the isotope ratio present in the gas. This is why it is possible to use a small ampoule of calibration gas for dilution with the ambient flow, instead of requiring a monitored flow of accurately diluted gas from the ampoule alone.

The carbon dioxide calibration gas contains a small added volume of $^{13}CO_2$. This added volume is calculated to be sufficient to cause the percentage of $^{13}CO_2$ in the carbon dioxide entering the breath tester to be very slightly higher than that expected from a negative patient, whose $^{13}CO_2$ ratio should be similar to that of the threshold level for ambient conditions. Typically, a value of 20 δ is used for the calibration procedure, where δ is 10 parts per million of $^{13}CO_2$. A patient's breath test is regarded as positive if his $^{13}CO_2$ to $^{12}CO_2$ ratio is 5 δ above the background threshold. A value of 20 δ thus enables a clear calibration to be made, yet at a level close to the typical detection levels demanded of the breath tester in normal use.

The calibration is performed by the use of a stream of flowing ambient air, which generally contains no more than 1000 ppm of $^{12}CO_2$ and 10 ppm of $^{13}CO_2$, to which is added a small volume of the calibrating gas. As an alternative, an ampoule full of ready mixed calibration gas at the correct dilution could be used, containing a sufficiently high volume of gas to fill the complete system. This, however, would make the calibration more costly, and would also result in a sudden rush of gas into the system as such a large volume of gas is released, which would make it difficult to operate at ambient pressure, without allowing the overpressure to dissipate, thus requiring an even larger volume of calibration gas. Furthermore, a container with 300 ml of gas, even if somewhat compressed,

would occupy valuable space in such an instrument, compared with a 9 ml sample.

Fig. 6A now shows an additional embodiment for performing the instrument calibration, in that the calibrator unit housing 90 incorporates two ampoules 92, 94 of calibration gas. In the first ampoule 92 is contained a quantity of natural carbon dioxide, whose volume is such that its release into the flow of air through the system will result in the predetermined percentage of CO_2 for the measurement system to operate optimally. The level of $^{13}CO_2$ contained is that of naturally occurring $^{13}CO_2$, and the release of the gas from inside the ampoule, such as by operation of the first plunger 96, or by any of the methods described hereinabove, enables a calibration of the base line of the measurements, against which all future measurements are made. The second ampoule 94 contains natural carbon dioxide calibration gas containing a small added volume of $^{13}CO_2$ in comparison to the gas in the first ampoule 92. This additional volume is sufficient to cause the percentage of $^{13}CO_2$ in the carbon dioxide entering the breath tester to be very slightly higher than that of the baseline, which contains no excess $^{13}CO_2$ above the naturally occurring level. Typically, a value of 20 δ is used. Once the baseline calibration has been performed, the second ampoule 94 is opened by means of plunger 98, and a calibration at the pre-chosen 20 δ level is performed. This embodiment therefore allows the measurement span of the breath tester to be correctly calibrated, in addition to the point calibration performed in the single ampoule embodiment. In use, the frequency of performance of a calibration check, as compared to the frequency of performance of a calibration verification will be determined by local conditions of use of the instrument.

Fig. 6B is a schematic drawing of an embodiment similar to that of Fig. 6A except that the gases from the two ampoules are preferably conveyed to the sampling line 78 in separate tubes 97, 99, in order to avoid any mixing of residual gas remaining from the first ampoule 92, when the second ampoule 94 is broken. Such mixing could interfere with an accurate calibration.

Reference is now made to Fig. 7, which illustrates schematically a further preferred embodiment of the calibration unit of a calibrating fluid filter device according to the present invention, especially useful for ^{13}C carbon dioxide breath tests. The sampling tube 100 is divided at some point along its length into two branches. One of these branches 102 is constructed of the same gas-impervious material as the sampling line, typically PVC. The other branch 104 is made of a material which behaves either as a selective membrane with selectively high penetration rate of CO_2 through its wall, or as a porous diffusive tube to the gas under test. The gas is directed through one or the other of these branches by means of a solenoid valve, or a mechanical valve 106, and then passes into the breath tester by means of an interface connector 108.

Fig. 8 now shows an example of such a porous diffusive tube 120, as could be used in the embodiment shown in Fig. 7, according to a preferred embodiment of the present invention. The gases flow through the tube from one end 124 to the other 126. The wall material 122 is made of a porous material chosen such that the gases flowing within, including carbon dioxide, undergo slow diffusion 128 out through the wall. As an example, the wall thickness of the porous section, its length and the flow rate of gas through it can be conveniently and preferentially chosen such that in passage down the porous section, forty percent of the carbon dioxide content diffuses out.

However, because of the different molecular weights of $^{13}CO_2$ and $^{12}CO_2$, the $^{13}CO_2$ diffuses out more slowly than $^{12}CO_2$ and the result is a small enrichment of the $^{13}CO_2$ level in the gas after its passage through the porous tube. The diffusion constant is inversely proportional to the square root of the molecular weight of the diffusing molecule. By means of simple mass diffusion calculations, it can be shown that the change ΔR in the ratio R of $^{13}CO_2$ to $^{12}CO_2$ in passage of the gas down such a porous tube is given by:

$$\Delta R = (R_{out} - R_{in}) = R_{in} * \Delta^{12}CO_2/^{12}CO_{2\,in} * [1 - \sqrt{M(^{12}CO_2) / M(^{13}CO_2)}]$$

where M ($^{12}CO_2$) is the molecular weight of $^{12}CO_2$ and M($^{13}CO_2$) that of $^{13}CO_2$,

$\Delta^{12}CO_2$ is the change in the percentage of $^{12}CO_2$ in passage down the tube, and $^{12}CO_{2\ in}$ is the percentage of $^{12}CO_2$ at the tube input.

Inserting values for M ($^{12}CO_2$) and M ($^{13}CO_2$), and assuming that a typical value of the ratio R_{in} at the tube input is 1.09×10^{-2}, ΔR can be given by:

$$\Delta R = 12.1 \times 10^{-5} \times (\Delta^{12}CO_2 / {}^{12}CO_{2\ in})$$

The breath tester is operated while inspiring exhaled breath through the impervious branch 102 of the sampling line. A baseline value of the level of $^{13}CO_2$ is obtained from this measurement, which for a healthy patient, will give a value close to the level of naturally occurring $^{13}CO_2$. The solenoid valve 106 is then switched to cause inspiration through the porous filter branch 104, and the measurement repeated.

As an example of the operation of this porous filter, according to a preferred embodiment of this invention, a tube 1.4 by 2.2mm in diameter, and 70 mm. in length is used. The average pore size is 0.37 μm. During passage down this tube, if the percentage of total CO_2 is reduced from 5% to 3%, i.e. by 0.4 of its initial value, then in accordance with the above expression for ΔR, the percentage of $^{13}CO_2$ in the sampled gas measured is reduced by 4.8×10^{-5}. This is equivalent to a change of 4.8 δ in the detected level of $^{13}CO_2$, thus enabling convenient calibration of the breath tester.

This calibration unit has an inherent advantage in that quite independently of any absolute calibration points or correction methods used in the breath tester, it provides an expected change in the level of $^{13}CO_2$ very similar in magnitude to the threshold level above which the breath test can be considered to give a positive result from the patient's samples. For this reason, quite apart from its use as a periodic calibration check of the breath tester, it could prove useful as a speedy sensitivity check of the instrument at any time, for determining whether a patient's results which are on the borderline of being considered positive, are being correctly measured by the instrument.

It should be understood that though this embodiment has been described in terms of preferential diffusion of isotopes of carbon dioxide, it is equally applicable to preferential diffusion of any gaseous isotopic cleavage product which appears in the exhaled breath of a patient. Each gas breath tested will in general require its own different porous material, to provide a suitable diffusion ratio for the gases measured.

For use in the complete calibrating device of the present invention, the calibration unit described in this embodiment may be combined with any of the interfaces or moisture filters described in the previously mentioned embodiments brought hereinabove.

It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the present invention includes both combinations and subcombinations of various features described hereinabove as well as variations and modifications thereto which would occur to a person of skill in the art upon reading the above description and which are not in the prior art.

CLAIMS

We claim:

1. A calibration device for use with a gas analyzer, comprising:

   a calibrating unit; and

   an enabling mechanism for enabling operation of said gas analyzer.

2. A calibration device for use with a gas analyzer according to claim 1 and wherein said enabling mechanism is operative to count the number of tests performed by said gas analyzer.

3. A calibration device for use with a gas analyzer according to claim 1 and wherein said enabling mechanism is operative to accumulate the time of operation of said gas analyzer.

4. A calibration device for use with a gas analyzer according to any of claim 1 to claim 3 and also comprising a filter for removing fluids from a gas to be analyzed.

5. A calibration device for use with a gas analyzer according to any of claim1 to claim 4 and wherein said enabling mechanism for enabling operation of said gas analyzer is operated by said calibrating unit.

6. A calibration device for use with a gas analyzer according to claim 4 and wherein said enabling mechanism for enabling operation of said gas analyzer is operated by said filter.

7. A calibration device for use with a gas analyzer according to any of claim 1 to claim 6 and wherein said enabling mechanism is communicative with said

gas analyzer by means of a signal selected from a group including electrical, electronic, optical, mechanical, magnetic and gaseous signals.

8. A calibration device for use with a gas analyzer, comprising:

a calibrating unit; and

a count actuating mechanism initiated by first use of said calibration device, operative to begin a count of the number of tests performed with said calibration device.

9. A calibration device for use with a gas analyzer according to claim 8 and also comprising a filter for removing fluids from the gas to be analyzed.

10. A calibration device for use with a gas analyzer according to claim 8 and wherein said count actuating mechanism is actuated by said calibrating unit.

11. A calibration device for use with a gas analyzer according to claim 9 and wherein said count actuating mechanism is actuated by said filter.

12. A calibration device for use with a gas analyzer according to any of claim 7 to claim 8 and wherein said count is used to prevent use of said gas analyzer after a predetermined number of tests have been performed.

13. A calibration device for use with a gas analyzer according to any of claim 8 to claim 11 and wherein said count of the number of tests performed with said calibration device is performed within the gas analyzer.

14. A calibration device for use with a gas analyzer according to any of claim 8 to claim 11 and wherein said count of the number of tests performed with said calibration device is performed within the calibration device.

15. A calibration device for use with a gas analyzer according to any of claim 8 to claim 14 and wherein said enabling mechanism is communicative with said gas analyzer by means of a signal selected from a group including electrical, electronic, optical, mechanical, magnetic and gaseous signals.

16. A calibration device for use with a gas analyzer according to any of claim 1 to claim 7 and wherein said calibrating unit releases a calibration gas of known composition into said gas analyzer.

17. A calibration device for use with a gas analyzer according to claim 16 and wherein said enabling mechanism is actuated by release of said calibrating gas.

18. A calibration device for use with a gas analyzer according to any of claim 8 to claim 15 and wherein said calibrating unit releases a calibration gas of known composition into said gas analyzer.

19. A calibration device for use with a gas analyzer according to claim 18 and wherein said count actuating mechanism is actuated by release of said calibrating gas.

20. A calibration device for use with a gas analyzer according to any of claim 1 to claim 7 and wherein said enabling mechanism is actuated by means of an active integrated circuit disposed on said calibration device

21. A calibration device for use with a gas analyzer according to any of claim 8 to claim 15 and wherein said count actuating mechanism is actuated by means of an active integrated circuit disposed on said calibration device

22. A calibration device for use with a gas analyzer according to any of claims 8 to 15 and claim 21, and also comprising a disenabling device which prevents said count actuating mechanism from being reinitiated after first use of said calibration device.

23. A calibration device for use with a gas analyzer according to either of claim 4 and claim 9 and wherein said filter is a section of a sampling tube having built-in fluid filtering properties.

24. A calibration device for use with a gas analyzer according to claim 20 and wherein said built-in fluid filtering properties are supplied by means of a drying agent disposed in proximity to at least part of an inside wall of said sampling tube.

25. A calibration device for use with a gas analyzer according to any of the previous claims and wherein the construction of said calibration unit and said fluid filter are such as to essentially maintain the waveform of a breath of gas to be analyzed.

26. A calibrating unit for use with a gas analyzer, comprising:

a sampling line for conveying a gas to be analyzed to said gas analyzer;

at least one enclosure housing at least one container of calibrating gas;

at least one mechanism for releasing said calibrating gas in said at least one container into said enclosure, said mechanism having interactive control contact with said gas analyzer; and

at least one delivery conduit connecting between said enclosure and said sampling tube for conveying said calibrating gas after release into said sampling line.

27. A calibration device for use with a gas analyzer according to claim 26 and wherein said interactive control contact comprises the actuation of said mechanism by means of said gas analyzer

28. A calibration device for use with a gas analyzer according to claim 26 and wherein said interactive control contact comprises the transmission of a signal to said gas analyzer on actuation of said mechanism.

29. A calibrating unit for use with a gas analyzer according to claim 26, and wherein said at least one container of calibrating gas comprises two containers of calibrating gas.

30. A calibrating unit for use with a gas analyzer according to claim 26, and wherein said at least one delivery conduit comprises two delivery conduits.

31. A calibrating unit for use with a gas analyzer, comprising:

a calibrating gas mixture comprising at least a first and a second gas; and

a delivery conduit for conveying said calibrating gas mixture to said gas analyzer, said delivery conduit comprising a material which allows preferential diffusion through its wall of at least one of said at least a first and a second gas.

32. A calibrating unit for use with a gas analyzer according to claim 31, and ~~wherein said material is a selective membrane.~~

33. A calibrating unit for use with a gas analyzer according to claim 31, and wherein said material is a porous diffusive tube.

34. A kit for calibration of a gas analyzer comprising at least one calibrating unit according to any of the previous claims, and a plurality of disposable sampling tubes for each of at least one calibrating unit.

35. A kit for calibration of a gas analyzer according to claim 34, and wherein at least one of said sampling tubes comprises a fluid filter.

36. A kit for calibration of a gas analyzer comprising:

at least one calibrating unit capable of interactive communication with said gas analyzer; and

a plurality of disposable sampling tubes for each of said at least one calibrating unit.

37. A kit for calibration of a gas analyzer according to claim 36, and wherein at least one of said sampling tubes comprises a fluid filter.

38. A calibrating unit operative to generate a second calibration material from a first material input thereto.

39. A calibrating unit according to claim 38 and wherein said first material is also a calibrating material.

40. A calibrating unit according to claim 38 and wherein said materials are gases for use in a gas analyzer.

41. A breath bringer which changes a characteristic during use.

42. A breath bringer according to claim 41, and wherein said characteristic is a color.

43. A calibration device for use with a gas analyzer according to claim 1 and

wherein said enabling mechanism is operative to accumulate the time since last calibration of said gas analyzer.

44. Apparatus according to any of the preceding claims and substantially as shown and described hereinabove.

45. Apparatus according to any of the preceding claims and substantially as shown and described in any of the drawings.

For the Applicant:

Sanford T. Colb & Co.,
Advocates and Patent Attorneys.
C:34070

FIG. 1

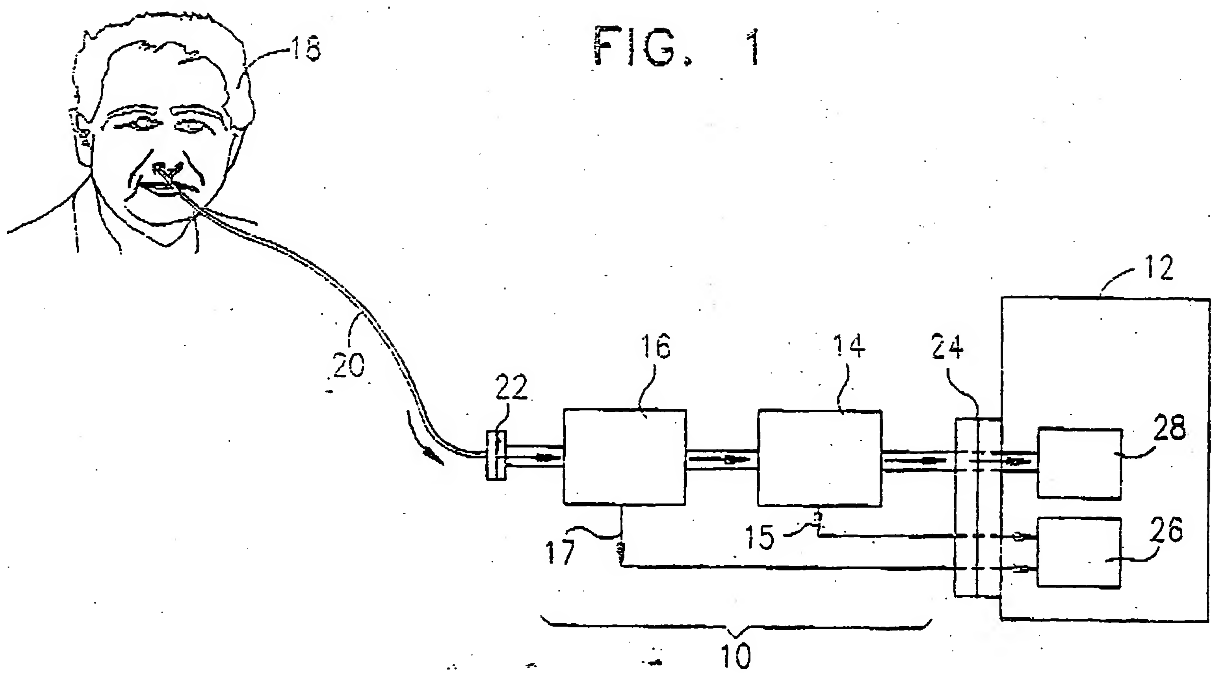


FIG. 2A

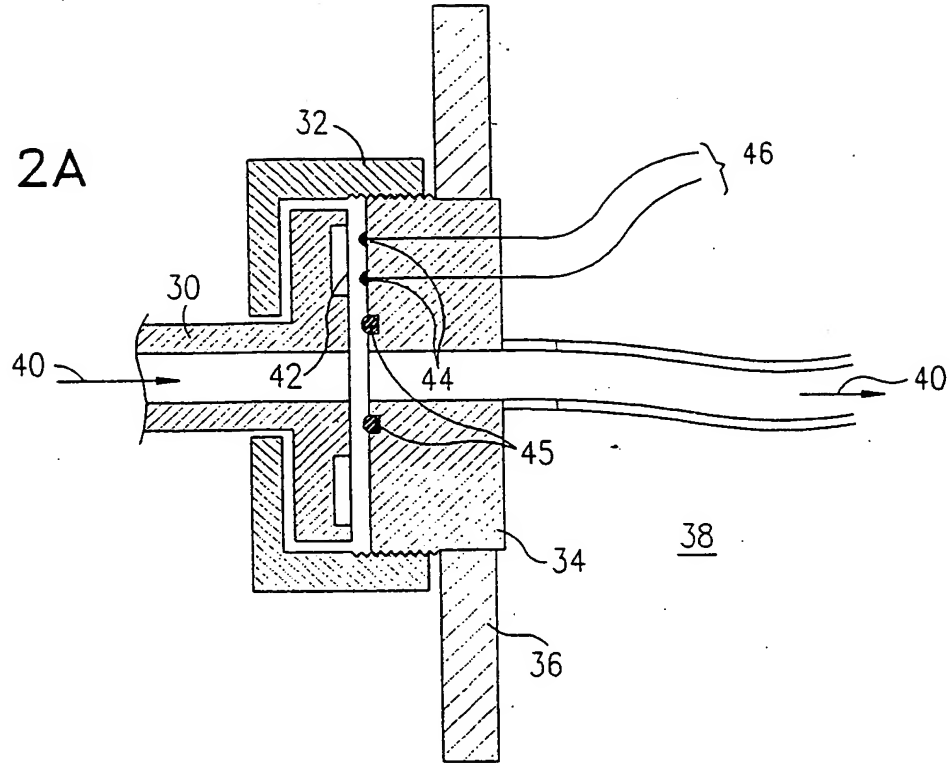


FIG. 2B

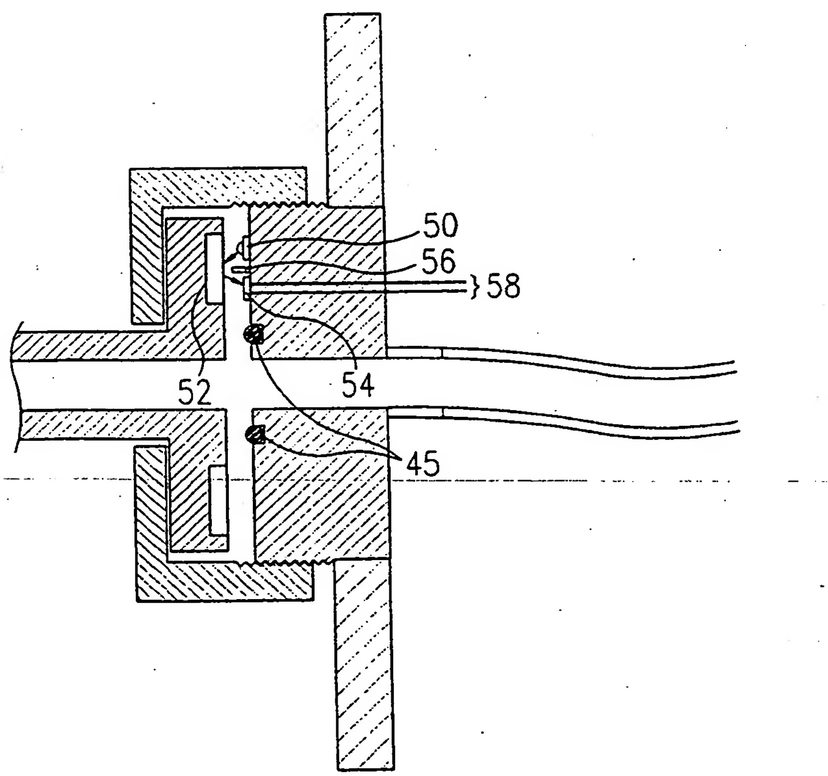
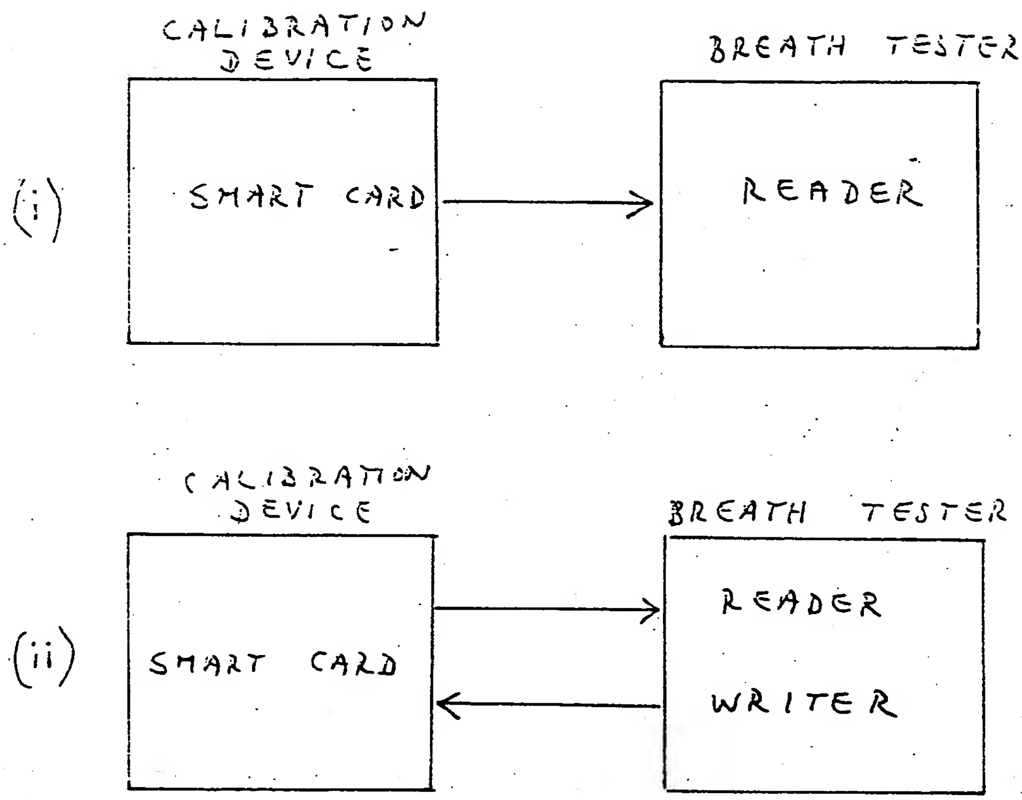


Fig 2C



(i)
CALIBRATION DEVICE
SMART CARD
BREATH TESTER
READER
(ii)
CALIBRATION DEVICE
SMART CARD
BREATH TESTER
READER
WRITER

FIG. 3

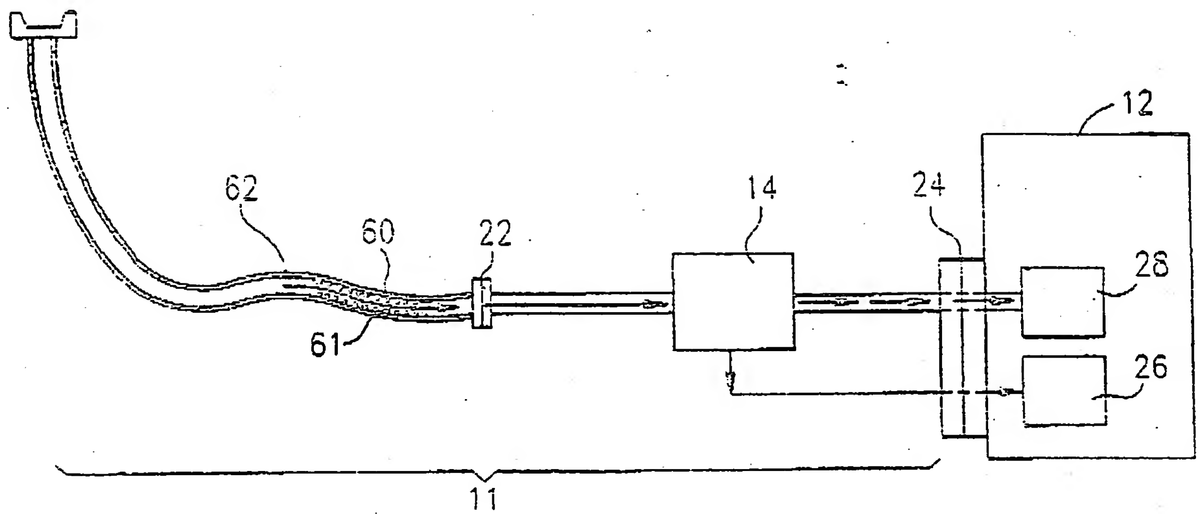
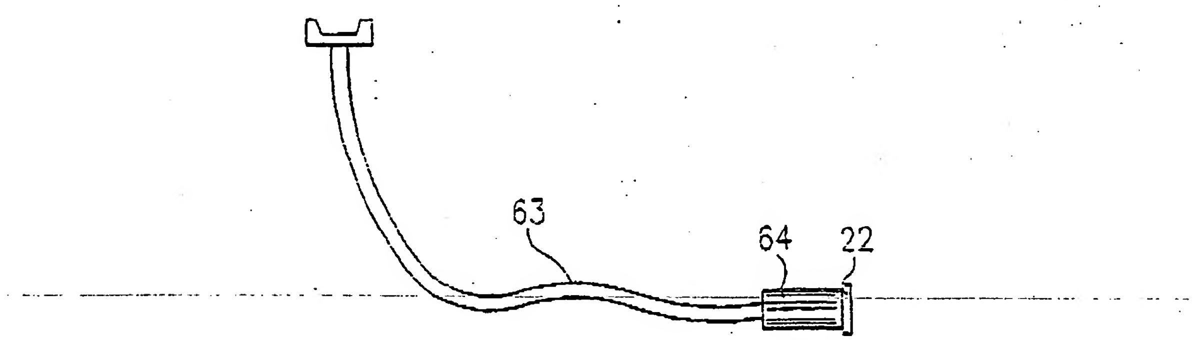


FIG. 4



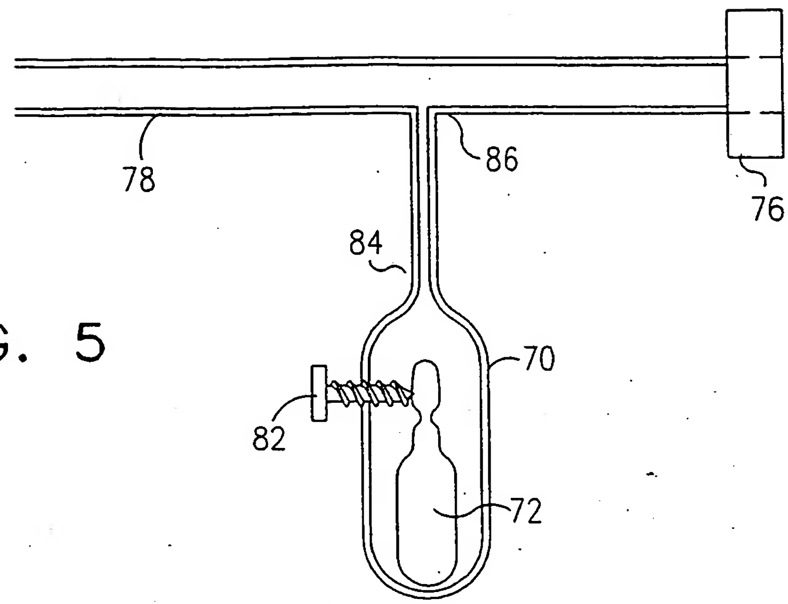


FIG. 5

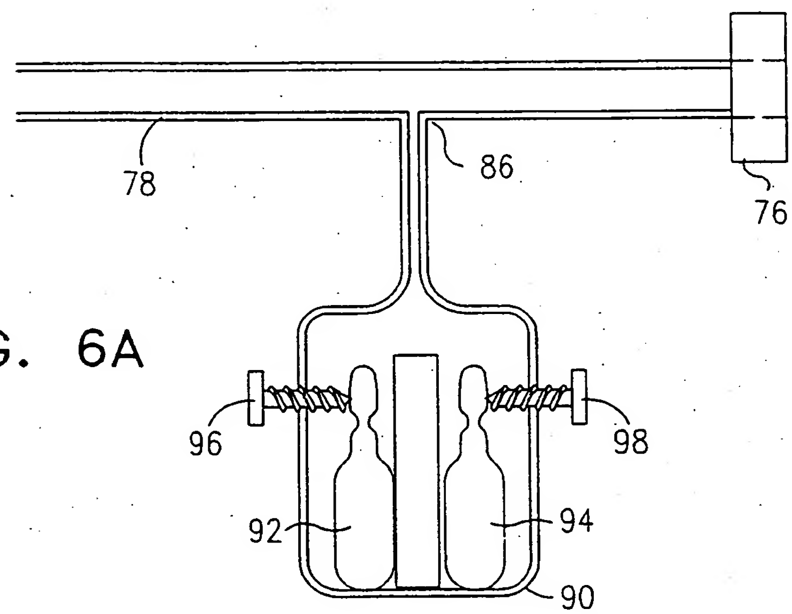


FIG. 6A

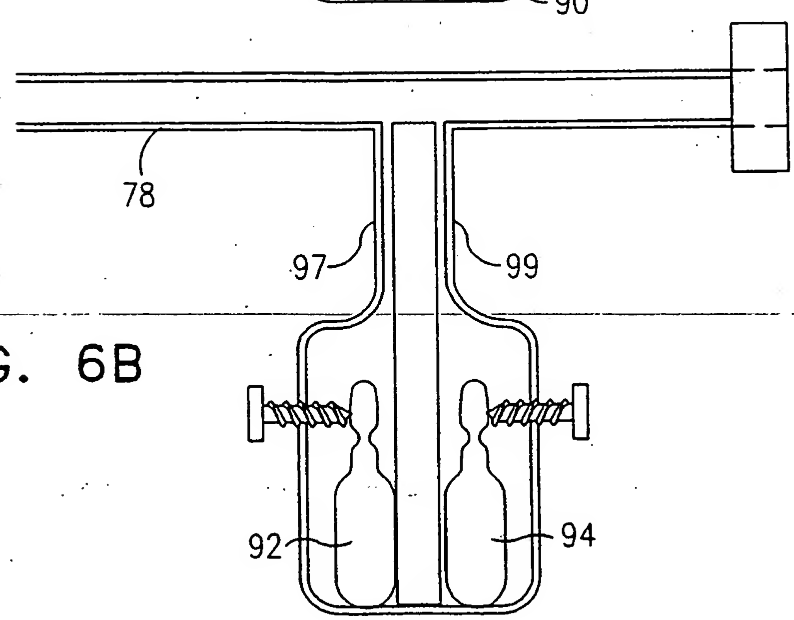


FIG. 6B

FIG. 7

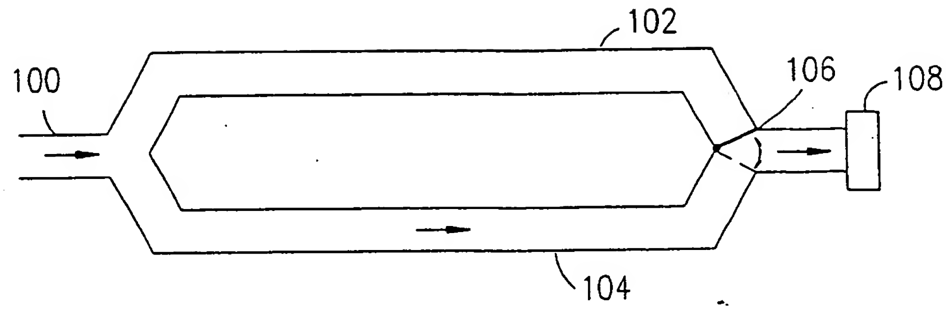


FIG. 8

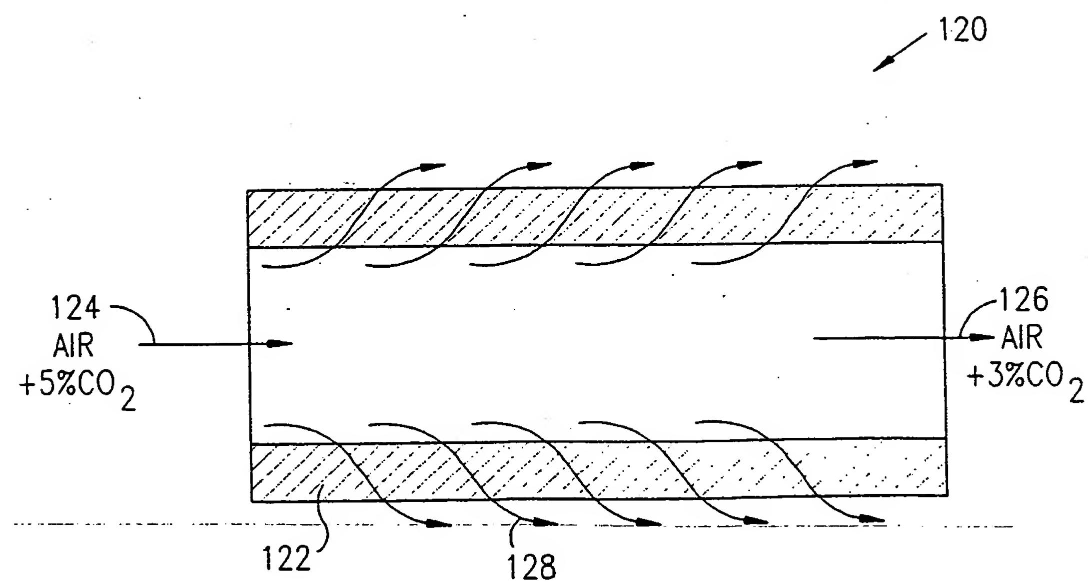


FIG. 9A

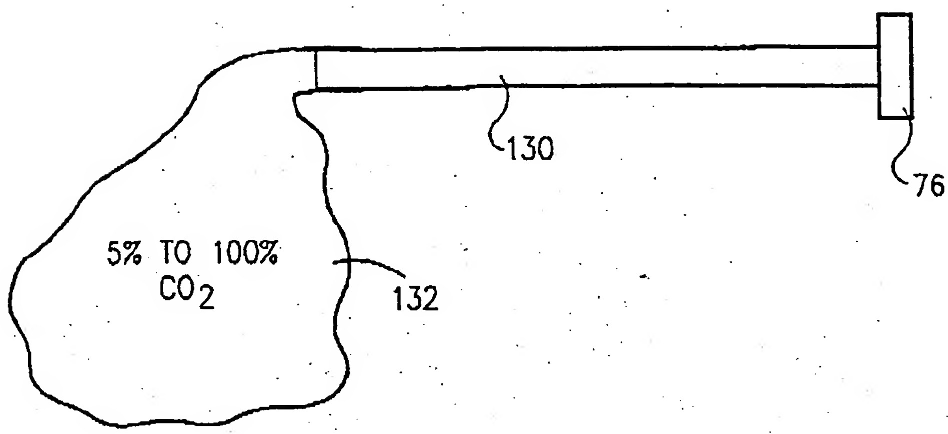


FIG. 9B